Barbiturate abuse and addiction and their relationship to alcohol and alcoholism

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The abuse of various drugs and chemicals has become a major concern of our contemporary society and is replacing sex as the number one topic in the public media. Alcohol is to some extent being pushed into the background by the more exotic agents and we tend to forget that alcoholism is still the most prevalent chemical dependency affecting our mature, potentially productive population. However, in this age of "chemical mind alteration" we became increasingly aware of the fact that people often do not confine themselves to the abuse of a single substance, and this is also true of many alcoholics. Among the various drugs that alcoholics may combine with alcohol, the barbiturates are the most common.

In this paper we attempt to give a brief review of barbiturate abuse in general and its relationship to alcohol and alcoholism in particular.

What are barbiturates?

Barbiturates are various derivatives of barbituric acid which were introduced into medicine in 1903 when the hypnotic action of diethylbarbituric acid (barbital; Veronal) was demonstrated by Fischer and von Mering. In 1912 phenobarbital became available, and since that time numerous varieties have appeared on the market. They all act as depressants of the central nervous system; in smaller doses they are used as daytime sedatives and in larger doses as hypnotics.

Barbiturates are generally classified according to the duration of their action (Table I).[1] The ultrashort-acting ones are used exclusively, when given by intravenous administration, as agents producing quick, superficial general anesthesia for short surgical procedures or induction of general anesthesia; they play no part in drug abuse. The short- and intermediate-acting barbiturates are the most widely prescribed sleeping pills and sedatives and the most frequently abused. Long-acting barbiturates, as well as being generally used as sedatives or hypnotics, are often employed as anticonvulsants; they are less often abused than the previous group.

Barbiturate abuse

Barbiturates are frequently prescribed even today, when as daytime sedatives they have become somewhat less popular since the introduction of the more expensive tranquillizers. A recent survey in Metropolitan Toronto[2] states that the hypnotic-sedative drugs, which are largely composed of barbiturates, are still in first place among all prescribed mood-modifying drugs; in fact, their consumption has steadily increased even in recent years. Barbiturates can be useful drugs, and many people are able to use them for years without ever abusing them. Those who do abuse them may do so in a pattern very similar to alcohol abuse; a one-night affair, a binge of a few days' or a few weeks' duration, or continuous use. When they are used continuously the development of tolerance may necessitate an increase in dosage, and withdrawal symptoms may appear upon abrupt discontinuation of the drug. In the latter case we justifiably describe the situation as one of physical dependence or addiction.

TABLE I
Classification of barbiturates

I. Ultrashort-acting	
Intravenous use only No abuse	Hexobarbital (Evipal) Thiopental (Pentothal)
II. Short- and intermediate-acting	
Effect: 2-6 hours Frequently abused	Pentobarbital (Nembutal) Secobarbital (Seconal) Amobarbital (Amytal) Butabarbital (Butisol)
III. Long-acting	
Effect: >6 hours Occasionally abused	Diethylbarbital, barbital (Veronal) Phenobarbital (Luminal)

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Barbiturate addiction

That frank addiction to barbiturates is a distinct possibility is well recognized today, although North America was slow to appreciate the fact despite the references to it in the European literature many years ago.[3-5]

Isbell[6] stated that if the daily dose exceeds 500 mg. continuously, physical dependence may occur, and if the dose is more than 800 to 900 mg. daily for at least 60 days, the patient will likely develop delirium and convulsions if the drug is suddenly withdrawn (Table II). In this situation some addicts may die, and this makes withdrawal from barbiturates more dangerous than withdrawal from opiates.

TABLE II
Relationship of barbiturate dose to addiction and tolerance

<500 mg./day	No addiction; tolerance may be complete
500-800 mg./day	Possible addiction
>800 mg./day for over 60 days	Addiction (severe withdrawal symptoms); tolerance never complete

Tolerance is the term applied when a drug gradually loses its effectiveness, so that the dose has to be increased in order to maintain the same effect. In the case of barbiturates, tolerance may be partly due to microsomal enzyme induction in the liver and partly to adaptation of the brain.[7] On a dosage of up to 500 mg. per day it is possible to develop nearly complete tolerance to the drug (Table II); that is, it becomes ineffective, so that an increase in the dosage is necessary. With a dosage of over 800 mg. per day, tolerance is never complete; some intoxication will always be present in individuals who take such high doses.[6] This distinguishes barbiturates from opiates, which can rapidly bring about very high and complete tolerance to doses which would be fatal to a novice. Neither barbiturates nor alcohol causes such a high and complete tolerance. The dose that would kill a novice would also kill an addict.

Barbiturates, besides having their known pharmacological effect, may cause intoxication that is very similar to that produced by alcohol, with motor incoordination, impaired thinking, lack of emotional control, aggressive behaviour, staggering, etc.

When the drug is suddenly discontinued, these symptoms of intoxication disappear in an addicted individual, and in the first eight to 12 hours the patient appears improved (which should not mislead the physicians and nurses). Later, nervousness, tremor, agitation and hypotension develop and as long as two to eight days after the abrupt discontinuation of the drug the patient is likely to have delirium and/or convulsions of the grand mal type.

Treatment of barbiturate withdrawal

From the foregoing it is obvious that if the daily dose of barbiturates exceeds 500 mg. per day over a period of 60 days, abrupt withdrawal is absolutely contraindicated. The patient should be stabilized on his own dose, preferably with a short-acting barbiturate such as pentobarbital (Nembutal), which is gradually reduced by not more than 100 mg. a day. With this routine, we have withdrawn all our barbiturate addicts smoothly. We also use prophylactic anticonvulsants, namely diphenylhidantoin (Dilantin) 100 mg. three times a day, although some authors view its usefulness as questionable.[8] One should not try to substitute other drugs for barbiturates in this situation. Phenothiazines will not only be ineffective, but they will not control convulsions and may even provoke them.[9] However, once the patient has been withdrawn and a long-term sedative is still required, phenothiazines are preferred because true addiction to them usually does not occur.

Patterns of barbiturate abuse

What we have just described applies largely to the person who has become physically dependent on barbiturates or addicted to them (taking 500 mg. or more daily for a prolonged period). However, not every case of barbiturate abuse is equivalent to addiction. Some people abuse these drugs only sporadically or for short periods, or manage to keep the dose relatively low, i.e. less than 500 mg. daily.

There are people who are so-called "pure" barbiturate abusers or addicts; that is, they do not use anything else. These may be patients for whom the drugs have been prescribed for legitimate reasons; after a time they find the original dose ineffective, and as their tolerance develops they gradually increase the dose until they may become physically dependent on the drug. This is more likely to occur in those who use barbiturates as daytime sedatives rather than as hypnotics. The reason for this can be found in the experimental work of Wahlström,[10] who reported that administration of barbiturates to sleeping animals produces little or no tolerance, while the same dose during waking activity causes rapid tolerance. Others clearly seek the intoxicating rather than the therapeutic effect of barbiturates. Not infrequently barbiturates are used in conjunction with opiates, particularly when the opiate supply is short. Barbiturates do not yet constitute a major problem in the subculture of drug-using young people, but they are often employed as marginal drugs, to suspend an LSD trip or to get "down" after amphetamine use.

Alcohol and barbiturates

Alcoholics are particularly prone to intermittent or continuous barbiturate abuse which sometimes may amount to frank addiction.[5] The alcoholic who is given a barbiturate by his doctor or by his buddy will be quick to recognize that its intoxicating effect is in many ways similar to and interchangeable with that of alcohol. Furthermore, it can greatly boost the alcohol effect. There will be some who eventually even abandon alcohol and turn to barbiturates entirely,[5] discovering that they have distinct advantages over alcohol—they are easy to carry and hide, they do not smell and do not upset the stomach.[8]

Addiction to barbiturates in alcoholics is but one potential danger. Even for the occasional barbiturate user, the synergistic or addi-

tive effect of the drug and alcohol represents inherent hazards. Teare[11] in England drew attention to, and provided evidence of, the possibility of "accidental suicide" by both substances when the confusion caused by either one results in an accidental overdose of the other. This is quite apart from the deliberate suicide attempt to which alcoholics are quite prone. Several other studies indicate the fatal synergism of alcohol and barbiturates[12-14] and emphasize that a considerable number of fatal barbiturate poisonings are accidental deaths where survival might have been possible if alcohol had not been present. A toxicological survey in Ontario in 1966 reported a great increase in cases in which both alcohol and barbiturates are implicated.[15] Doenicke[16] calls attention to the increased impairment of driving ability when both alcohol and barbiturates are present in the body, so that their combined use has to be regarded as an increasing causative factor in traffic accidents. This was demonstrated by the studies of Gupta and Kofoed[15] and of Forney.[17] However, Smart, Schmidt and Bateman[18] showed in their series that persons using alcohol and barbiturates had fewer accidents than the computed expectancy; in their view this might be due to the fact that barbiturates were more often taken at night when driving was less likely.

The mechanism by which alcohol and barbiturates react with each other is not entirely clear, but considerable research material on this subject is available in this field. Forney and Hughes[19] summarized the various studies that advanced evidence regarding both synergistic or simple additive effects of alcohol and barbiturates. Fraser and his associates[20] observed that large amounts of alcohol may partially suppress the more serious manifestations of barbiturate withdrawal, the reason being that these two intoxications are to some degree equivalent. Seidel[21] demonstrated that pre-treatment with ethanol deepens and prolongs pentobarbital anesthesia in mice. Melville, Joron and Douglas[22] showed that the disappearance of barbiturates from the blood is slowed down in the presence of alcohol.

In alcoholics we have to consider the interesting phenomenon of cross-tolerance, which means that the development of tolerance to one depressant drug (e.g. alcohol) produces increased tolerance to another (e.g. barbiturate) even though the second substance may never be administered. This would account for the fact (which every anesthetist knows) that standard doses of barbiturates have little effect on alcoholics.[23] It also explains why alcoholics tend to use higher than usual doses of these drugs from the beginning. Frahm, Löbkens and Soehring[24] showed a massive reduction of barbiturate effect in guinea-pigs forced to drink 10% alcohol for seven weeks. Cross-tolerance might occur in one of two ways. One is a metabolic cross-tolerance, as suggested by some investigators.[25, 26] This view assumes a common metabolic pathway for alcohol and barbiturates, and on this basis the person who chronically takes alcohol would eliminate barbiturates faster, and vice versa. On the other hand, Khanna and Kalant[27] do not think that this is true *in vivo;* in their opinion the mechanism involves a cellular tolerance in the central nervous system. Similar observations were made by Hatfield,[28] who also ruled out the presence of liver microsomal enzyme induction as the mechanism responsible for cross-tolerance, because of increased (rather than decreased) plasma drug levels in the ethanol-tolerant animal. But there may be common metabolic pathways as borne out by the work of Graham, Carmichael and Allmark[29] and that of Giarman, Flick and White,[30] who reported that the duration of thiopental (Pentothal) anesthesia can be greatly increased by disulfiram (Antabuse), although Jepsen and Korner[31] challenged this statement.

Another factor to be considered in alcoholics is that in temporary impairment of liver function (e.g. fatty liver) or in permanent liver damage (e.g. cirrhosis) the metabolism of barbiturates suffers. The result is that in these conditions the opposite of cross-tolerance is produced, namely barbiturate toxicity with relatively small doses. This is particularly true of the shorter-acting barbiturates, which are exclusively metabolized in the liver. The long-acting ones, such as phenobarbital, are largely excreted by the kidney.[7]

All complex experimental data support the clinically accepted observations that alcohol and barbiturates do not mix well and that barbiturates should have no place in the treatment of alcoholism (except, of course, when one withdraws an alcoholic from barbiturates). Koppanyi, Canary and Maengwyn-Davies[32] have described a case of respiratory arrest and death when an agitated alcohol-intoxicated patient was given a therapeutic dose of intravenous amobarbital (Sodium Amytal). In the alcohol-withdrawal syndrome there are still some who prefer barbiturates.[33] Although one cannot say that the short-term medical administration of these drugs is necessarily dangerous in situations such as delirium tremens, or that they will induce abuse, we see no need for their use in such cases as there are other drugs which are equally effective.[34] We agree with Glatt's suggestion[5] that in alcoholics, if a hypnotic is necessary, a non-barbiturate preparation should be preferred, for the latter is less likely to be habit-forming or addicting. One instance where a barbiturate, such as phenobarbital, may be justified in the management of an acutely ill alcoholic is the treatment of withdrawal convulsions, although more recently intravenous diazepam (Valium) has been advocated as the drug of choice for interrupting seizures.[35] As far as long-term, prophylactic anticonvulsant therapy is concerned, phenobarbital is frequently used, especially in conjunction with diphenylhydantoin (Dilantin). However, the work of Cucinell *et al.*[36] indicated that this combination may not be an ideal one, since phenobarbital may enhance the rate of metabolism of diphenylhydantoin through enzyme induction (at least in dogs), resulting in a decreased effect. This observation awaits confirmation in man.[37] These interesting problems of drug interactions were recently well reviewed by Hunninghake.[38]

We certainly would discourage the use of barbiturates as sleeping pills or daytime sedatives in the long-term treatment of alcoholics. Unfortunately, many physicians, either not knowing that they are dealing with an alcoholic or unaware of the potential risks, often willingly prescribe them for the shaky, nervous patient who complains of insomnia. Repeat prescriptions, frequently given over the telephone, are not difficult to obtain, either because the doctor does not bother to check when he ordered the last supply or naïvely accepts such explanations as that the 100 tablets prescribed last week were accidentally dropped into the toilet. When the need eventually exceeds the quantity that one doctor can provide, getting multiple prescriptions from several doctors and filling them in various pharmacies is a readily available technique. The medical profession's contribution to drug abuse through lax prescribing habits cannot be dismissed lightly, even if one disagrees with Farber's[39] statement that "doctors are the greatest pushers" of some drugs today. In a hospital situation, as Holmes[8] pointed out, indirectly the nursing profession is responsible for many patients' first exposure to barbiturates as hypnotics. The nurses like to see all their charges asleep at night; thus—needed or not—they almost ritually request a routine order for a sedative, which is usually a barbiturate; the house staff, in their desire to please, eagerly comply. But doctors are not the only suppliers. Barbiturates are relatively easy to obtain on the black market, although at a higher price than in drug stores, and eventually this is where the regular abuser or addict obtains his supply.

The incidence of barbiturate abuse in general and in alcoholics in particular is not well established. In the few studies reported in the literature, barbiturates predominated as the main target for drug abuse in alcoholics. Chelton and Whisnant[40] found that about 70% of alcoholic drug-abusers had barbiturates in their urines when tested by chromatography. Ravnsborg[41] of Norway reported that in a hospitalized male alcoholic population approximately 22% misused various drugs and more than half of these took barbiturates. In one of Glatt's series from the United Kingdom,[5] 28% of 200 middle-class male alcoholics and 40% of 68 female alcoholics abused drugs, and almost all had taken barbiturates. We have done our own survey on the alcoholic patients of our medical unit, which is a hospital admitting a fairly representative cross-section of the alcoholic population. The results of this survey are reported in a separate paper.[42]

The problems we have discussed are practical ones. Since a sizable proportion of alcoholics also abuse other drugs, especially barbiturates:

1. One must be judicious in using various drugs and avoid prescribing barbiturates for known or suspected alcoholic patients.

2. One must probe diligently for a history of drug use and abuse in alcoholics.

3. Treatment of an alcoholic individual will be modified if there is evidence of drug use, particularly barbiturate dependence.

References

1. Goodman LS, Gilman A, editors: *Pharmacological Basis of Therapeutics*, third ed, New York, Macmillan, 1965.
2. Cooperstock R, Sims M: *Amer J Public Health*, In press
3. von Muralt L: *Z ges Neurol Psychiat* 22: 123, 1914
4. Pohlisch K, Panse F: *Schlafmittelmissbrauch*, Leipzig, Georg Thieme Verlag, 1934
5. Glatt MM: *Bulletin on Narcotics* 14: 19, 1962
6. Isbell H: *Bulletin of the Association of Food & Drug Officials of USA* 23: 35, 1959
7. Sherlock S: *Diseases of Liver and Biliary System*, fourth ed, Oxford, Blackwell, 1968
8. Holmes SJ: *Addictions* 9: 25, Spring, 1963
9. Seevers MH: *Postgrad Med* 37: 45, 1963
10. Wahlstrom G: *Acta Pharmacol (Kobenhavn)* 26: 92, 1968
11. Teare RD: *Medicoleg J* 34: 4, 1966
12. Bogan J, Smith H: *J Forensic Sci* 7: 37, 1967
13. Jetter WW, McLean R: *Arch Path (Chicago)* 36: 112, 1943
14. LeBreton R, Garat J: *Ann Med Leg (Paris)* 45: 78, 1965
15. Gupta RC, Kofoed J: *Canad Med Ass J* 94: 863, 1966
16. Doenicke A: *Arzneimittelforschung* 12: 1050, 1962
17. Forney RB: Combined effect of ethanol and other drugs, in *Prevention of Highway Injury*, edited by Selzer, ML, Gikas PW, Huelke DF, Ann Arbor, Highway Safety Research Institute, University of Michigan, 1967, p 70
18. Smart RG, Schmidt W, Bateman K: *Journal of Safety Research* 1: 67, 1969
19. Forney RB, Hughes FW: *Combined Effects of Alcohol and Other Drugs*, Springfield, Charles C Thomas, 1968
20. Fraser HF, Wikler A, Isbell H, et al: *Quart J Stud Alcohol* 18: 541, 1957
21. Seidel G: *Quart J Stud Alcohol* 29: 1004, 1968 (abstract)
22. Melville KI, Joron GE, Douglas D: *Toxic Appl Pharmacol* 9: 363, 1966
23. Soehring K, Schuppel R: Interactions between alcohol and drugs, in *Alcohol and Alcoholism*, edited by Popham RE, Toronto, University of Toronto Press, 1970, p 73
24. Frahm M, Lobkens K, Soehring K: *Arzneimittelforschung* 12: 1055, 1962
25. Rubin E, Lieber CS: *Science* 162: 690, 1968
26. Remmer H, Schuppel R: Influence of ethanol on drug metabolism, in *Alcohol and Alcoholism*, edited by Popham RE, Toronto, University of Toronto Press, 1970, p 80
27. Khanna JM, Kalant H: *Biochem Pharmacol*, In press
28. Hatfield GK: *Quart J Stud Alcohol* 29: 190, 1968 (abstract)
29. Graham WD, Carmichael EJ, Allmark MG: *J Pharm Pharmacol* 3: 497, 1951
30. Giarman NJ, Flick FH, White JM: *Science* 114: 35, 1951
31. Jepson NP, Korner B: *Acta Pharmacol (Kobenhavn)* 8: 418, 1952
32. Koppanyi T, Canary JJ, Maengwyn-Davies GD: *Quart J Stud Alcohol* (Suppl 1): 24: 1961
33. Bates RC: *Mich Med* 65: 449, 1966
34. Devenyi P: *Addictions* 14: 1, Winter, 1968
35. Librium and Valium: *Med Lett Drugs Ther* 11: 81, 1969
36. Cucinell SA, Koster R, Conney AH, et al: *Pharmacol Exp Ther* 141: 157, 1963
37. Kutt H, Haynes J, McDowell FH: *Neurology (Minneap)* 15: 274, 1965 (abstract)
38. Hunninghake DB: *Postgrad Med* 47: 71, 1970
39. Farber LH: Lecture delivered to the 52nd Interstate Postgraduate Medical Assembly, Chicago, Nov 7, 1967
40. Chelton LG, Whisnant CL: *Southern Med J* 59: 393, 1966
41. Ravnsborg IS: *Quart J Stud Alcohol* 26: 347, 1965 (abstract)
42. Devenyi P, Wilson M: *Canad Med Ass J* 104: 219, 1971